## BREAKING ADVANCES

**Highlights from Recent Cancer Literature**

**REVIEW**

**Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy**
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

## MEETING REPORT

**Ion Channels and Transporters in Cancer: Pathophysiology, Regulation, and Clinical Potential**
Stine F. Pedersen and Christian Stock

## PRIORITY REPORTS

**G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin**
Juanqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher

**Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network**
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui

## CLINICAL STUDIES

**Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein–Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients**

*Précis: Vaccination of nasopharyngeal carcinoma patients targeting two pathogenic viral antigens produces potent immune responses after they have completed chemo/radiotherapy.*

**Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model**
Sanitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jurgen K. Willmann

*Précis: This study lays the foundation for the development of a novel ultrasound-based imaging approach for earlier detection of breast cancer and paves the way for translational clinical trials in the future.*

**Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response**
David L. Masica and Rachel Karchin

*Précis: New methods are offered to improve the identification of drug response biomarkers in cancer cells.*

## INTEGRATED SYSTEMS AND TECHNOLOGIES

**Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model**
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## MICROENVIRONMENT AND IMMUNOLOGY

**Therapeutic Efficacy of Bifunctional siRNA Combining TGF-β1 Silencing with RIG-I Activation in Pancreatic Cancer**
Jonathan Ellermeier, Jiwu Wei, Peter Duewell, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr

*Précis: The potency of a therapeutic siRNA can be increased by a parallel strategy to combinatorially activate an RNA helicase that triggers inflammatory responses to double-stranded viral RNA with implications for understanding how to reprogram the tumor microenvironment to destroy tumor cells.*
LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis
Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Ho, Georgina Lang, and Janine T. Erler

Precis: The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

 Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma

Precis: HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.

 IFN-\(\gamma\)-Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence
Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin

Precis: By helping resolve an inflammatory response, IFN\(\gamma\) blockade can promote tumor regression by reprogramming the inflammatory microenvironment.

 Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth
Devika Gunasamy, Jerilyn K. Gray, Peterson Pathrose, Rishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz

Precis: This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.

 HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients
Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsig, Stine Kiaer Larsen, Tobias Wienefeldt Klausen, Inge Marie Svane, and Mads Hald Andersen

Precis: PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.

A Chimeric Receptor with NKG2D Specificity Enhances Natural Killer Cell Activation and Killing of Tumor Cells
Yu-Hsiang Chang, John Connolly, Noriko Shimasaki, Kousaku Mimura, Koji Kono, and Dario Campana

Precis: Findings illustrate how to increase the antitumor efficacy of NK cell therapy, a strategy that may be used to fight nearly any kind of human cancer.

Transcription Factor YY1 Contributes to Tumor Growth by Stabilizing Hypoxia Factor HIF-1\(\alpha\) in a p53-Independent Manner
Shourong Wu, Vivi Kasim, Mitsunobu R. Kano, Sayaka Tanaka, Shinshuke Obha, Yutaka Miura, Kanjiro Miyata, Xueying Liu, Ako Matsuhashi, Ung-il Chung, Li Yang, Kazunori Kataoka, Nobuhiro Nishiyma, and Makoto Miyagishi

Precis: Findings suggest a mechanistic strategy to block a core hypoxia-driven progression pathway regardless of p53 status.

Arkadia Regulates Tumor Metastasis by Modulation of the TGF-\(\beta\) Pathway
Marco A. Briones-Orta, Laurence Levy, Chris D. Madsen, Debiipriya Das, Yigit Erker, Erik Sahai, and Caroline S. Hill

Precis: An E3 ubiquitin ligase in the TGF-\(\beta\) signaling pathway is not required to regulate tumor growth but to colonize metastasis sites, suggesting novel antimeetastatic strategies.

Phosphorylation of Ribosomal Protein S6 Attenuates DNA Damage and Tumor Suppression during Development of Pancreatic Cancer
Abed Khalaileh, Avigail Dreazen, Areej Khatib, Roy Apel, Avital Swisa, Norma Kidess-Bassir, Anirban Maitra, Oded Meyuhas, Yuval Dor, and Gideon Zamir

Precis: Findings reveal that a key mTOR effector molecule is crucial for initiation of K-Ras-induced pancreatic cancers, illuminating the centrality of this mTOR pathway to evade p53-mediated tumor suppression in this setting.
**PREVENTION AND EPIDEMIOLOGY**

**MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non–Small Cell Lung Cancer Patients**
Xia Pu, Jack A. Roth, Michelle A.T. Hildebrandt, Yuanqing Ye, Hua Wei, John D. Minna, Scott M. Lippman, and Xifeng Wu

**Precise:** This large study of non-small cell lung cancer suggests that miRNA-related polymorphisms can predict clinical outcomes at a level that may be superior to other markers developed previously.

**GENETIC VARIATION IN TRANSFORMING GROWTH FACTOR ETA 1 AND MAMMOGRAPHIC DENSITY IN SINGAPORE CHINESE WOMEN**
Eunjung Lee, David Van den Berg, Chris Hsu, Giske Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Strat, Mimi C. Yu, and Anna H. Wu

**Precise:** Host genetic polymorphisms in a key growth factor in breast cancer may help identify women at an increased risk of breast cancer.

**IDENTIFICATION OF INHERITED GENETIC VARIATIONS INFLUENCING PROGNOSIS IN EARLY-ONSET BREAST CANCER**
Sajjad Rafiq, William Tapper, Andrew Collins, Sofia Khan, Ioannis Politopoulos, Sue Gerty, Carl Blomqvist, Fergus J. Couch, Heli Nevanlinna, Jianjun Liu, and Diana Eccles

**Precise:** This study maps host genetic variations that affect risks of poor prognosis in early onset breast cancer patients, with implications for how aggressive treatments should be used to improve survival outcomes.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors**
Ryian Alkins, Alison Burgess, Milan Ganguly, Giulio Francia, Robert Kerbel, Winfried S. Wels, and Kullervo Hynynen

**Precise:** Noninvasive MR-guided focused ultrasound allows targeted natural killer cells to circumvent the blood-brain barrier and treat HER2-amplified breast metastasis in the brain.

**Caveolin–1–LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer**
Salahaldin A. Tahir, Guang Yang, Alexei Goltsov, Ki-Duk Song, Chengzhen Ren, Jianxiang Wang, Wenjun Chang, and Timothy C. Thompson

**Precise:** This study offers mechanistic insights into how aerobic glycolysis is increased in prostate cancer, possibly revealing critical targets for effective antimetabolic therapy in this setting.
ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.